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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,184	SANDS ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendments/Remarks filed 10/25/05 are acknowledged. Claims 1-4 and 6-36 are included in the prosecution of this application. Claim 5 stands cancelled.

Claim Rejections - 35 USC § 112

The rejection of claims 1-4 and 6-36 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendment of 10/25/05 removing the new matter.

The rejection of claims 13 and 17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment of 10/25/05.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-8, and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haynes (4725442) in view of Burke (5552156).

Haynes states microdroplets are known and consist of spheres of organic liquid phase

drug approximately 500 Angstroms in diameter and range from 200 Angstroms up to at least one micron (10,000 Angstroms) in diameter and are covered with a monolayer of a suitable phospholipid. Haynes teaches microdroplets (200 angstroms up to a micron) of water insoluble drugs containing a pharmaceutically acceptable liquid surrounded by a layer of phospholipid, which are suitable for injection (Note the abstract, columns 2-8, and claims).

Although Haynes discloses his invention using anesthetics in examples, according to Haynes the microdroplets of the invention can be used to deliver **any water-insoluble/oil-soluble drug compound** via injection. See col. 1, lines 26-39. Moreover, Haynes teaches anti-cancer agents as the drugs which can be practiced in his invention. Note col. 8, lines 27-28 and claim 15.

The substantially water-insoluble drug is dissolved in a compatible, pharmaceutically acceptable organic liquid selected from an alkane, a dialkyl ether, a long-chain ester, a hydrophobic ester, a biocompatible silicone, a biocompatible high molecular weight fluorocarbon, an oil-soluble vitamin and a volatile liquid anesthetic. See column 5, lines 9-55 and claims 2-3.

Haynes teaches using various lipids in preparing the microdroplets. Further, Haynes teaches mixtures of two or more such lipids are useful to vary the surface properties and reactivity. The lipids taught are lecithin, including the instantly claimed lecithin, cholesterol, etc (col. 5 and 6, line 56 to line 50). Lastly, Haynes teaches mixing the microdroplets with an injectable vehicle, which is an isotonic solution. See claim 5. For instance, lecithin may be used in an amount of 1.28%. See column 9, lines 55-60.

Hayes does not specifically teach camptothecins as the anti-cancer drug.

Burke teaches camptothecin drugs encapsulated by lipids to overcome the insolubility and instability problems of camptothecin for intravenous administration. Burke teaches camptothecin is an anti-cancer drug that is water-insoluble that hinders its delivery to cancer cells. See column 1, lines 30-45. Burke states that camptothecin drugs bind the lipid bilayer of liposomes with great affinity and intercalates between the acyl chains of the lipid. Thus, the lactone ring of the camptothecin membrane bound drug is removed from the aqueous environment *inside* and *outside* of the liposome and is protected from hydrolysis, preserving the activity of the drug. Further, Burke teaches reducing the internal pH of the liposome to prevent hydrolysis of certain camptothecin drugs. See column 3, line 59 to column 4, line 2. Burke teaches the liposomes are stable are an external pH of 7.4 and 5. See column 21, lines 1-3. Thus, the lipid encapsulation creates an internal environment with a low pH to prevent hydrolysis of camptothecin drugs. (Note abstract). Various drug concentrations are utilized in the examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Haynes and Burke and utilize the instant camptothecin in Haynes's microdroplets. One would have been motivated to do with the expectation of similar results since firstly since Burke teaches camptothecin is a water-insoluble anti-cancer drug and Haynes clearly teaches the incorporation of any water-insoluble drugs including chemotherapeutic agents. Secondly, a skilled artisan would have reasonably expected success since Burke teaches the advantages of encapsulating water-insoluble camptothecin in phospholipid structures, which allows one to successfully deliver camptothecin by overcoming instability and insolubility problems caused by hydrolysis by the aqueous phase. Therefore, one

would have expected success since Haynes's microdroplets also encapsulate the water-insoluble drug and prevent contact with the aqueous phase.

With regard to claims 6-7, a skilled artisan would have been motivated to utilize the instant pH of less than 6 for the injectable carrier since Burke teaches a low pH prevents hydrolysis of camptothecin's lactone ring, thus preserving its activity. Therefore, a skilled artisan would have been motivated to simultaneously also manipulate the pH of the injectable carrier if camptothecin is utilized as the active of choice, to preserve its activity.

With regard to claims 13-17, it is within the skill of an artisan to manipulate the concentration of camptothecin using the guidance provided by Burke since Burke teaches several concentrations of camptothecin. Further, this is deemed to be a manipulatable parameter, which is known to those skilled in the art.

Response to Arguments

Applicant argues that to establish prima facie obviousness there must be some motivation either in the reference in the knowledge generally available to modify the reference. Applicant argues that the prior art reference must teach all the claim limitations. Applicant argues that the instant lipids are membrane forming and do not have a proclivity for converting to micelle structures at the concentrations used in the invention. Applicant argues that the lipid selected are chosen for the membrane forming properties and the desired results, which the reference do not disclose. Applicant argues Haynes teaches a monolayer of phospholipid microdroplet what would be a micelle. Applicant argues that Burke teaches solubilizing the camptothecin drug in a liposome or micelle composed of surfactants. Applicant argues the examiner has used improper hindsight.

Applicant's arguments filed 10/25/05 have been fully considered but they are not persuasive. The examiner is confused with applicant's arguments that Haynes microdroplets are different from the instant invention since they form micelles and the applicant's utilizes specific lipids for their tendency to not form micelles. The examiner notes the only criteria the applicant claims with regard to the lipid selection is that it is "phospholipids [that is] membrane forming". The examiner points out that Haynes's microdroplets is a drug surrounded by a phospholipids membrane layer. Note claim 25 which is directed to "microdroplets of from about 200 Angstroms to one micron in diameter produced by sonification and consisting of a water-insoluble local anesthetic or a solution thereof as the core stabilized against coalescence and surrounded by a phospholipid membrane layer". Further, the examiner refers to the instant specification to teach these asserted "special lipids" that do not readily form micelles. The instant specification page 18-19 lists certain lipids with this criteria such as for instance lecithin, sphingomyelin, phosphatidic acid, phosphatidyl serine, phosphatidyl inositol, cardiolipidn, phosphatidyl glycerol, steroids (cholesterol), etc. The examiner points to column 6 wherein Haynes teaches the same lipids. Further, the examiner notes that Haynes does not state that the microdroplets are micelles as applicant asserts, in fact nowhere is the word "micelle" found; particularly in column 2, line 52 to column 3, line 65 that applicant's cites to support the applicant's position.

Applicant asserts that the lipids are selected in certain concentrations, however the examiner notes that the independent claims do not recite any concentrations and thus applicant's arguments are based on features that are not in the independent claims. However, for arguendo

sake, the examiner points out that Haynes teaches lecithin in an amount of 1.28% for instance on column 3, line 59.

Applicant argues there is not suggestion to combine and that the examiner relies on a vague reference to Haynes "anabolic steroids in cancer chemotherapy" to reject the claims. However, applicant argues that camptothecin is not a steroid and possesses special properties.

It is pointed out that the examiner has not made an equivalency argument that anabolic steroids are equivalent to the instant camptothecin; the examiner recognizes the difference. The examiner further notes that to establish prima facie obviousness, a suggestion to modify the invention must exist. The examiner points out that Haynes teaches that the phospholipids microdroplets are suitable to deliver water-insoluble drugs that are centrally acting agents. Additionally, Haynes states that the list of drugs are illustrative and not meant to be limiting". See column 8, line 39. Further, Haynes envisages chemotherapeutic drugs in claim 15. The only teaching missing in Haynes is the specific use of camptothecin. However, the examiner points out that camptothecin is a water-insoluble drug that is a chemotherapeutic drug. Thus, the examiner relies on Burke to teach that camptothecin in particular. Burke teaches camptothecin is sensitive to water and encapsulating in lipids solves this instability. Thus, this is clear suggestion for one to utilize camptothecin in Haynes's lipid microdroplets since Haynes teaches the phospholipids microdroplets are useful for delivering 1) water-insoluble drugs and 2) Haynes suggests chemotherapeutic drugs. Burke provides further motivation to utilize the instant cancer drug.

The applicant argues that Burke teaches the use of liposomes and thus there is not suggestion to combine. Firstly, the examiner points out that Burke is utilized for the specific

teaching of camptothecin and not for the lipid vesicle since Haynes is not deficient in this sense. The examiner points out that Burke teaches camptothecin is an anti-cancer drugs and water-insoluble, the criteria set forth by Haynes for the selection of the drug. Thus, this argument is moot. However for arguendo sake, the examiner points out that the claims do not exclude a liposome since the broad term "microdroplet" encompasses liposomes. Moreover, the examiner points out that Burke teaches that camptothecin have greater affinity for the lipids and bind to the lipids and thus are not in contact with the aqueous phase inside and outside the liposome. Thus, clearly Burke teaches that it is preferable the interaction of water and camptothecin. Thus, providing a motivation to combine Haynes and Burke since Haynes teaches lipid encapsulation without an aqueous phase since the internal compartment of the microdroplet contains a water-insoluble liquid.

With regard to applicant's assertion that all the elements in the claim are not met, the examiner points out that Haynes teaches a microdroplets of from about 200 Angstroms to one micron in diameter, wherein the drug is contained in a water-insoluble liquid, and a phospholipids membrane layer. Further, the microdroplets are administered in a pharmaceutically acceptable liquid carrier such as saline, i.e. to make an aqueous suspension. The only teaching lacking is the instant drug. The examiner relies on Burke to cure this deficiency. Therefore, all elements of the claimed invention are taught.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the

time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claims 9-11 and 18-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haynes cited above in view of Burke cited above, further in view of WO 99/61001.

As set forth above, Haynes discloses microdroplets (200 angstroms up to a micron) of water insoluble drugs containing a pharmaceutically acceptable liquid surrounded by a layer of phospholipid (Note the abstract, columns 2-8, and claims). Haynes teaches using various lipids in preparing the microdroplets. Further, Haynes teaches mixtures of two or more such lipids are useful to vary the surface properties and reactivity. The lipids taught are lecithin, including the instantly claimed lecithin, cholesterol, etc (col. 5 and 6, line 56 to line 50). Haynes teaches sterile injectable compositions. See claim 25.

As set forth above, Burke teaches claimed camptothecins encapsulated in a lipid structure and a low pH to preserve its activity.

Haynes and Burke do not teach the inclusion of tonicity modifiers (mannitol or trehalose) as claimed in independent claims 18-19 or thermally sterilizing the composition as claimed in dependent claims 9-11.

WO 99/61001 discloses suspensions of submicron and micron sized particles of water insoluble biologically active substances that are stabilized by thermoprotecting agents and that can be terminally steam sterilized without any significant increase of mean particle size. These compositions display markedly reduced heat-induced coagulation, flocculation, or particle size growth during the terminal steam sterilization process. WO teaches it is necessary to sterilize

parenteral composition. However, during this process surfactants on the surface of the particle are released. The particles that are devoid of the surfactant become unstabilized and grow in size. See pages 1-2. WO's invention is directed to stabilizing particles that utilize only phospholipids as surfactants. Specifically egg lecithin (Lipoid) is disclosed. See Table 1. Examples of suitable thermoprotecting agents include one or a combination of pharmaceutically acceptable water-soluble polyhydroxy compounds that also act as tonicity modifiers such as dextrose, sucrose, mannitol, sorbitol, and lactose. The reference teaches including these agents for protection during sterilization (note the abstract, examples and claims).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and include tonicity modifiers such as trehalose or mannitol in the composition. One would have been motivated to do so since WO teaches that the instant sugars are thermoprotectants and protect the phospholipid particle suspensions during sterilization.

Response to Arguments

Applicant argues that since Haynes and Burke do not teach or suggest the instant invention, the rejection should be withdrawn.

Applicant's arguments filed10/25/05 have been fully considered but they are not persuasive. The merits of Haynes and Burke have been set forth above and thus the rejection is maintained.

Pertinent Art

US 6,497,896 and US 6,53,080 are made of record.

Conclusion

All the claims are rejected at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER